

wherein the presence of differential expression indicates that test cell has an IBD or pre-IBD phenotype.

29. (Currently amended) A method for determining **[the] an IBD or pre-IBD** phenotype of a test cell from a given tissue, comprising detecting the presence or absence of differential expression, relative to a **[normal] control** cell of the given tissue type, of at least 25 different genes shown in Table 1,

wherein the presence of differential expression indicates that test cell has an IBD or pre-IBD phenotype.

REMARKS

Claims 5 to 7 and 19 to 29 are pending and presently under examination.

Regarding the Declaration

Applicant appreciates the Examiner's reconsideration and entry of the new Declaration filed on February 6, 2003.

Regarding the Rejection under 35 U.S.C. § 112, first paragraph

Applicant respectfully traverses the rejection of claims 5 to 7 and 19 to 29 under 35 U.S.C. § 112, first

paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. In making the rejection, the Examiner notes that the claims are drawn to methods of determining the phenotype of a test cell by detecting differential expression of at least 5 genes from Table 1. However, rather than relying on the genes of Table 1 themselves, the Examiner indicates that the claimed methods use probes (nucleic acid sequences) which are similar, identical or complementary to the genes of Table 1. According to the Examiner, the claimed methods lack sufficient written description since probes identical or complementary to the genes in Table 1 have to be identified or prepared and, further, arranged in array format.

Applicant submits that the specification provides written description sufficient to convey to one skilled in the relevant art that the inventor was in possession of the claimed invention at the time the application was filed. In considering the following arguments, the Examiner is respectfully requested to keep in mind that patent laws specify that an invention must be sufficiently described but not necessarily exemplified in a patent specification.

The specification provides written description sufficient to describe means for "detecting the presence or absence of differential expression," including but not limited to, description of suitable nucleic acid probes. The specification discloses that cells can be obtained from a

subject and the levels of the disclosed biomarkers, protein or mRNA levels, determined using techniques such as Northern analysis, reverse transcription-polymerase chain reaction (RT-PCR), *in situ* hybridization, immunoprecipitation, Western blot hybridization or immunohistochemistry (page 42, lines 2-8; page 43, lines 18-29). As further described in the specification, a nucleic acid probe useful in the claimed methods hybridizes under stringent conditions to a sequence shown in Table 1 or a sequence complementary thereto and can be, for example, at least about 80% or 100% identical to, for example, at least 12, 15, 25, 40 or more nucleotides of one of the IBD gene set shown in Table 1 or a sequence complementary thereto (specification at page 3, lines 26-32). Thus, the specification provides a precise definition of nucleic acid probes suitable for "detecting the presence or absence of differential expression" in the methods of the invention. In sum, by describing the GenBank accession numbers in Table 1 corresponding to gene sequences, and further describing sequence identities, such as at least 80% or 100% identities, and lengths of nucleic acid probes useful in the invention, the specification clearly conveys to one skilled in the art that Applicant was in possession of probes suitable for practicing the claimed invention.

Insofar as the Examiner appears to suggest that the specification does not describe how to arrange or prepare probes in array format, Applicant would point out that the claimed methods do not recite detection using probes in an array format and can be practiced using a variety of techniques and formats including RT-PCR, Northern analysis, western analysis and

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immunohistochemistry. Furthermore, in regard to nucleic acid arrays, the specification teaches their construction and use at page 45, line 33, to page 46, line 1. Thus, sufficient written description is provided in regard to nucleic acid arrays.

In sum, Applicant submits that the specification satisfies the written description requirement and respectfully requests that the Examiner remove the rejection of claims 5 to 7 and 19 to 29 under the first paragraph of 35 U.S.C. § 112.

Regarding the Rejections under 35 U.S.C. § 112, second paragraph

The rejection of claims 5 to 7 and 19 to 29 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite is respectfully traversed.

Regarding the phrase "relative to a normal cell"

Claims 5 to 7 and 19 to 29 stand rejected as allegedly vague and indefinite due to the phrase "relative to a normal cell." The Examiner requests clarification as to whether the cell is 'normal' as compared to a specific cell or condition or as compared to expression of specific genes.

Applicant submits that the claims are clear and definite as written in view of the specification. In particular, in view of the specification, one skilled in the art understands that the recited "normal cell" is an appropriate

control cell, for example, from a cell line or individual without apparent symptoms or risk for an inflammatory bowel disease or disorder. In this regard, the specification teaches that differentially expressed genes were identified by comparison of gene expression in tissue from an animal without apparent symptoms or risk of an inflammatory bowel disease or disorder as compared to gene expression in tissue from an animal which has symptoms of, or risk of developing, an inflammatory bowel disease or disorder (page 2, lines 1-9). As further set forth in the specification, the level of a marker polypeptide in a test cell can be compared with the level of marker polypeptide in a "control cell" such as a normal cell or a transformed cell of known phenotype (page 44, lines 9-13; page 6, lines 18-21). Thus, in view of the specification, the claims are clear to one skilled in the art. Nevertheless, in order to further prosecution of the subject application, Applicant has amended the claims to recite that the comparison is relative to "a control cell," which is a cell of known phenotype without apparent symptoms or risk for an inflammatory bowel disease or disorder.

In view of the above remarks and amendments, Applicant respectfully requests that the Examiner reconsider and remove this ground for rejecting claims 5 to 7 and 19 to 29 under 35 U.S.C. § 112, second paragraph.

Regarding the phrase "phenotype of a test cell" and
antecedent basis for "the phenotype"

The claims further stand rejected due to an alleged lack of clarity of the phrase "phenotype of a test cell."

Applicant submits that the claims are clear and definite as written and that the term "phenotype" is well known in the art to mean anything that is part of the observable structure, function or behavior of a living organism. Furthermore, in view of the concluding phrase of the independent claims reciting that the presence of differential expression indicates that the test cell has an "IBD or pre-IBD phenotype," it is clear that the phrase "phenotype of a test cell" refers to those phenotypic characteristics which distinguish an IBD cell or pre-IBD cell from another cell. While Applicant maintains that the claims are clear and definite as written, Applicant herein amends the preamble of independent claims 5, 28 and 29 to recite a method for determining "an IBD or pre-IBD phenotype" of a test cell in order to further prosecution of the subject application. In view of the above remarks, Applicant respectfully requests that the Examiner remove this ground for rejection.

Claims 5, 28 and 29 also stand rejected as allegedly lacking sufficient antecedent basis for "the phenotype." While maintaining that the claims are clear as written, the preamble of claims 5, 28 and 29 has been amended to recite "an IBD or pre-IBD phenotype." In view of the above remarks and

amendments, the Examiner is respectfully requested to remove this ground for rejection.

Regarding the phrase "presence or absence of differential expression"

The Examiner asserts that the meaning of the phrase "differential expression" is not clear.

Applicant submits that the claims are clear and definite as written and that the meaning of the phrase "differential expression" is clear to one skilled in the art. In particular, the phrase "differential expression" is well known to those skilled in the art as referring to gene expression in a first sample which is different as compared to expression of the same gene in a second sample. This meaning of the phrase "differential expression" is corroborated by the specification, which teaches that an assay for detecting differential expression of at least one gene can be an assay which "detects a difference in the level of expression" (page 2, lines 15-22). The meaning of the phrase is further corroborated by the specification at page 5, line 30, to page 6, line 1, which teaches that IBD cells can be identified or classified by the upregulation or downregulation of expression of particular genes, alterations in protein levels or modification, or changes at the genomic level such as mutation or methylation. In addition, the specification further teaches that methods of determining the phenotype of a test cell can be practiced using, for example, a nucleic acid probe to detect the mRNA of a test cell or, for example, using an antibody specific for the gene

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product of a nucleic acid represented in Table 1 to assay the proteins of a test cell (page 42, line 25, to page 43, line 9). In sum, in view of the specification and what is well known to those skilled in the art, the term "differential expression" is clear and definite. Accordingly, Applicant respectfully requests that the Examiner remove this ground for rejecting the claims under 35 U.S.C. § 112, second paragraph.

Regarding an alleged lack of essential steps

Claims 5 to 7 and 19 to 29 also stand rejected under the second paragraph of § 112 as allegedly incomplete for omitting essential steps. In this regard, the Examiner asserts that the claimed methods do not recite how or which phenotype of the cell is determined and do not make clear how detecting differential gene expression is related to the phenotype of the test cell.

Applicant respectfully submits that the claims are clear and definite as written, particularly in view of the concluding phrase of independent claims 5, 28 and 29, which recites that the presence of differential expression indicates that said test cell has an IBD or pre-IBD phenotype. From this concluding phrase, it is clear that the presence of differential expression correlates with an IBD or pre-IBD phenotype and, thus, that the presence of differential expression serves to indicate a particular phenotype of the test cell. To further clarify these claims, the preamble of the claims has been amended to specify the phenotype determined, i.e. an "IBD or pre-IBD phenotype." In view of the above remarks, Applicant

submits that claims 5 to 7 and 19 to 29 are complete as written, and respectfully requests that this ground for rejection be removed.

Regarding the Rejections under 35 U.S.C. § 102(b)

The §102(b) rejection over Alexander et al.

The rejection of claims 5 to 7, 19 to 21 and 24 to 28 under 35 U.S.C. §102(b) as allegedly anticipated by Alexander et al. is respectfully traversed. The cited reference by Alexander et al. allegedly anticipates the claimed invention by describing altered expression of proto-oncogenes in patients with inflammatory bowel disease as compared to the expression of these genes in control colon epithelial cells.

Each of the rejected claims is directed to a method for determining the phenotype of a test cell from a given tissue by detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1, as recited in independent claims 5 and 28. While the cited reference appears to characterize expression of several protooncogenes (*H-ras*, *c-myc*, *c-fos*, *c-jun*, *junB*, *myc*, *c-abl*, *c-yes* and *p53*), Alexander et al. do not teach detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1. Applicant emphasizes that the claims as written do not refer to "other IBD genes" but instead relate to at least 5 different genes shown in Table 1. Given that Alexander et al. report analysis of protooncogenes but do not describe detecting at least 5 different genes shown in Table 1, the cited reference does not teach each and every element of the claim and therefore cannot anticipate the claimed invention.

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In view of the above remarks, Applicant respectfully requests that the Examiner reconsider and remove the rejection of claims 5 to 7, 19 to 21 and 24 to 28 under 35 U.S.C. §102(b) as allegedly anticipated by Alexander et al.

The §102(b) rejection over Dieckgraefe et al.

The rejection of claims 5 to 7 and 19 to 29 under 35 U.S.C. §102(b) as allegedly anticipated by Dieckgraefe et al. is respectfully traversed.

Dieckgraefe et al. allegedly report using a GeneChip expression monitoring system for examination of mucosal gene expression in ulcerative colitis, Crohn's disease and non-IBD specimens. The Office Action indicates that Dieckgraefe et al. observe dramatic changes in expression of a wide range of genes, and that this reference further reports identification of specific marker genes useful for diagnosis and analysis of disease activity and particular features of histology.

Applicant maintains that the cited abstract by Dieckgraefe et al. cannot anticipate claims 5 to 7 and 19 to 29, which each relate to detecting the presence or absence of differential expression of at least 5 different genes shown in Table 1. At best, Dieckgraefe et al. report identification of different classes of genes including, for example, cell adhesion molecules and reparative factors, and further assert that genes which can act as specific markers were identified. However, Dieckgraefe et al. do not describe at least 5 different genes

shown in Table 1, or detecting the presence or absence of differential expression of such at least 5 different genes as recited in the present invention. Dieckgraefe et al. therefore do not teach each and every element of the claims.

In particular, the cited abstract does not contain an enabling disclosure, which is required in order for a patent or publication to constitute an anticipatory reference (*Chester v. Miller*, 906 F.2d. at 1576 n.2, 15 U.S.P.Q.2d. at 1336 n.2 (Fed. Cir. 1990)). Dieckgraefe et al. do not place the invention in the possession of the public by teaching how to make and use the claimed invention. Specifically, Dieckgraefe et al. do not teach the identity of at least 5 different genes shown in Table 1 of the subject application. Thus, one skilled in the art would not have had the guidance necessary to, for example, obtain or prepare five different probes or antibodies suitable for detecting differential expression of at least 5 different genes shown in Table 1. Because one skilled in the art, in view of Dieckgraefe et al., would not have known which "at least 5 different genes" to analyze for differential expression, the cited abstract does not contain an enabling disclosure. Consequently, Dieckgraefe et al. cannot anticipate the claimed invention.

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CONCLUSION

In view of the above remarks, Applicant respectfully requests that the Examiner reconsider and remove the rejection of claims 5 to 7 and 19 to 29 under 35 U.S.C. §102(b) as allegedly anticipated by Dieckgraefe et al. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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